APAP31191-A 072852.0117
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Seo Hong Yoo			
Serial No.	:	09/778,154	Examiner	:	Kim, Vickie
Filed	:	February 5, 2001	Group Art Unit	:	1615
For	:	PREPARATION OF AQUEOUS CLEAR SOLUTION DOSAGE FORMS WITH BILE ACIDS			

DECLARATION OF SEO HONG YOO UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, SEO HONG YOO, hereby declare as follows:

1. I am the sole inventor of the invention disclosed and claimed in the above-captioned European patent application.

2. Claims 138-148 now pending in the instant application relate to particulate-free aqueous solutions comprising a soluble bile acid and a hydrolytic product of starch.

3. I have reviewed and understand the disclosures of Japanese Patent No. 62153220A to Satoshi (hereafter, "Satoshi") including the professional English translation enclosed herewith as Exhibit 1.

FIRST SET OF EXPERIMENTS

4. Under my direction and control, the following first set of experiments were conducted to assess the stability of the solutions of Satoshi and the solutions of the present invention. Stability was measured as set forth in the Examples of the instant application. *See e.g.* Yoo application at p. 30, lines 16-19 and p.32, lines 1-8. Stability tests were performed on the following compositions:

(A) Satoshi

(i) In accordance with Example 1 of Satoshi, 0.1 g of Ursodeoxycholic acid (UDCA) was dissolved in 1 mL of pure ethanol. This was combined with 80 mL of sterilized water. Then 3 g of amylodextrin was added and the resulting suspension (total volume; 100 mL) was heated (60-65° C) with stirring. The extractives of Satoshi's Example 1 were not added to this solution due to their strong color, which may have interfered with subsequent visual inspection of physical appearance of the solution, iodine-based assay for amylodextrin (USP 24/NF 19 page 2220), identification of UDCA with sulfuric acid & formalin (The Japanese Pharmacopoeia 13th Edition), and HPLC analysis of precipitate.

(ii) In accordance with Example 1 of Satoshi, 0.1 g of ursodeoxycholic acid (UDCA) was dissolved in 1 mL of pure ethanol. This was combined with 80 mL of sterilized water. Then 3 g of maltodextrin was added and the resulting suspension (total volume;

100 mL) was heated (60-65° C) with stirring. The extractives of Satoshi's Example 1 were not added to this solution due to their strong color, which may have interfered with subsequent visual inspection of physical appearance of the solution, iodine-based assay for amylodextrin, identification of UDCA with sulfuric acid & formalin, and HPLC analysis of precipitate.

(iii) A third Satoshi-like solution was prepared. As in paragraph 4(a)(i) above, 0.1.g of UDCA was dissolved in 1 mL of pure ethanol. In this solution, however, 2 g of amylodextrin in 10 mL of water was added next. Then, in accordance with USP 24 & NF 19 page 2220, a copy of which is enclosed herewith, boiling water was added to make 100 mL. The whole solution was boiled for 2 minutes ("Satoshi-like UDCA+amylodextrin solution").

(iv) A fourth solution was prepared exactly as in (iii) above except the UDCA/ethanol mixture was omitted ("amylodextrin-only solution").

(B) Yoo

(i) A solution was prepared in accordance with Example 3 of the instant application. Specifically, 100 mg of UDCA was dissolved in 2 mL of 0.5% NaOH solution (this NaOH solution was prepared by combining NaOH with pure water) with stirring to make a UDCA sodium salt solution. *See e.g.* Yoo application at Example 9. Then, 2.5 g of maltodextrin and pure water were added to the clear

UDCA sodium salt solution with stirring at room temperature to make 100 mL of a mixed solution. The pH of this mixed solution was above 9.7. This strong alkaline solution was treated with acid (mineral acid or organic acid) to adjust the pH of the solution (pH 1, pH 3, pH 5, pH 7, pH 8, pH 8.5 and pH 9). As soon as the solution was treated with acid, it became clear without any precipitation or cloudiness at any pH.

5. All solutions were sealed in transparent glass bottles after they were prepared and kept at room temperature in the dark (UDCA and carbohydrate in solution are sensitive to sunlight). The physical appearance of the solutions was visually inspected periodically.

6. The following results were obtained in a first experiment and confirmed in a second, wholly independent experiment:

(A) Satoshi

(i) During preparation of the UDCA+amylodextin solution [paragraph 4(a)(i) above], the combination of the UDCA/ethanol mixture with 80 mL of water resulted in a milky solution. Upon heating, the solution with amylodextrin became mostly clear with some undissolved matter. After the solution cooled to room temperature, the solution appeared opalescent or turbid. The insoluble material settled to the bottom of the bottle with time. Substantial quantities of precipitation were visible at 2-4 weeks after the solution was prepared. After 3-4 months the clear solution (supernatant) again

became cloudy and then, substantial precipitated material was observed at the bottom of the bottle at 4-5 months after the solution was prepared.. The presence of UDCA and amylodextrin in the precipitated matter was confirmed by iodine test of amylodextrin, identification of UDCA with sulfuric acid & formalin, and HPLC.

(ii) During preparation of the UDCA+maltodextrin solution [paragraph 4(a)(ii) above], the combination of the UDCA/ethanol mixture with 80 mL of water resulted in a milky solution. Upon adding maltodextrin and stirring, the solution became mostly clear with some undissolved matter. The initial turbidity observed upon cooling in the UDCA+amylodextrin solutions was not observed here. However, the solution became cloudy after 3-4 months at pH 5.5 and room temperature. Like the UDCA+amylodextrin solution, after 4-5 months the UDCA+maltodextrin solution was cloudy and substantial precipitated material was visible at the bottom of the bottle.

(iii) Both the amylodextrin-only solution [paragraph 4(a)(iv) above] and the Satoshi-like UDCA+amylodextrin solution [paragraph 4(a)(iii) above] were almost clear when hot. Upon cooling, however, both solutions became opalescent or turbid in spite of the use of considerablely less amylodextrin than that of Satoshi (2 g instead of 3 g). The opalescent material then settled to the bottom of the bottles leaving a mostly clear supernatant. Both solutions again

became cloudy after 3-4 months and a month or later, the insoluble material agglomerated and precipitated. The Satoshi-like UDCA+amylodextrin solution [paragraph 4(a)(iii) above] showed substantially more precipitated material than that of the amylodextrin-only solution [paragraph 4(a)(iv) above]. UDCA in the precipitated material was detected by the identification method with sulfuric acid and formalin.

(b) Yoo

(i) Solutions prepared according to Example III of the instant application [paragraph 4(b)(i) above] did not show any visible precipitation at pH 1, pH 3, pH 5, pH 7, pH 8, pH 8.5 and pH 9 at room temperature up to 20 weeks (5 months), at which time the experiment was terminated.

7. As seen above, the solutions according to Example III of the instant invention display significantly higher stability than the Satoshi solutions. Contrary to the text of Satoshi, particulate-free solutions were not obtained by following the methods of Satoshi, *e.g.* Example 1.

SECOND SET OF EXPERIMENTS

8. Under my direction and control, the following experiments were conducted to assess the stability of the solutions of Satoshi and the solutions of the present invention. Stability was measured as set forth in the Examples of the instant application. *See e.g.* Yoo application at p.30, lines 16-19.

9. Stability tests were performed on the compositions described below. Unless otherwise indicated, the compositions were prepared according to the method described in paragraph [16] of Satoshi. However, since this paragraph does not indicate whether or not the samples were heated during preparation (*i.e.* discloses mixing at 20-65° C), both heated and unheated compositions were prepared and tested. In addition, in an attempt to be more thorough, several variations of the Satoshi compositions were prepared as indicated below.

(A) Satoshi Sample 23

(i) A composition was prepared in accordance with Satoshi Sample 23 without heating (20° C) during mixing.

(ii) A composition was prepared in accordance with Satoshi Sample 23 with heating (up to 65° C) during mixing and subsequent cooling to room temperature.

(iii) A composition was prepared in accordance with Satoshi Sample 23 with heating (up to 65° C) during mixing and subsequent cooling to room temperature. Unlike Satoshi Sample 23, however, this composition was prepared with 100 mg less ursodeoxycholic acid (UDCA) (*i.e.* 900 mg instead of 1000 mg).

(iv) A composition was prepared in accordance with Satoshi Sample 23 with heating (up to 65° C) during mixing and subsequent cooling to room temperature. Unlike Satoshi Sample 23, however, this composition was prepared with 200 mg less UDCA (*i.e.* 800 mg instead of 1000 mg).

(B) Satoshi Sample 22

(i) A composition was prepared in accordance with Satoshi Sample 22 without heating (20° C) during mixing.

(ii) A composition was prepared in accordance with Satoshi Sample 22 with heating (up to 65° C) during mixing and subsequent cooling to room temperature.

(C) Satoshi Sample 20

(i) A composition was prepared in accordance with Satoshi Sample 20 with heating (up to 65° C) during mixing and subsequent cooling to room temperature.

(D) Satoshi Sample 19

(i) A composition was prepared in accordance with Satoshi Sample 19 with heating (up to 65° C) during mixing and subsequent cooling to room temperature. Unlike Satoshi Sample 19, however, this composition was prepared with 200 mg less UDCA (*i.e.* 400 mg instead of 600 mg).

(E) Satoshi Sample 18

(i) A composition was prepared in accordance with Satoshi Sample 18 with heating (up to 65° C) during mixing and subsequent cooling to room temperature. Unlike Satoshi Sample 18, however, this composition was prepared with 200 mg more UDCA (*i.e.* 300 mg instead of 100 mg).

(F) Satoshi Sample 15

(i) A composition was prepared in accordance with Satoshi Sample 15 without heating (20° C) during mixing.

(G) Satoshi Sample 15

(i) A composition was prepared in accordance with Satoshi Sample 15 without heating (20° C) during mixing.

(ii) A composition was prepared in accordance with Satoshi Sample 15 without heating (20° C) during mixing. Unlike Satoshi Sample 15, however, this composition was prepared with 100 mg less UDCA (*i.e.* 400 mg instead of 500 mg).

(H) Satoshi Sample 22

(i) A composition was prepared in accordance with Satoshi Sample 22 without heating (20° C) during mixing.

(ii) A composition was prepared in accordance with Satoshi Sample 22 without heating (20° C) during mixing. Unlike Satoshi Sample 22, however, this composition was prepared with 100 mg more UDCA (*i.e.* 700 mg instead of 600 mg).

(iii) A composition was prepared in accordance with Satoshi Sample 22 without heating (20° C) during mixing. Unlike Satoshi Sample 22, however, this composition was prepared with 200 mg more UDCA (*i.e.* 800 mg instead of 600 mg).

(I) Satoshi Sample 23

(i) A composition was prepared in accordance with Satoshi Sample 23 without heating (20° C) during mixing. Unlike Satoshi Sample 23,

however, this composition was prepared with 100 mg less UDCA (*i.e.* 900 mg instead of 1000 mg).

(ii) A composition was prepared in accordance with Satoshi Sample 23 without heating (20° C) during mixing.

(J) Reference

(i) In each case, the Satoshi samples were compared to a reference solution prepared by adding an amount of the sodium salt of UDCA equivalent to 0.1 mg of UDCA to pure water. Upon formation of a clear solution, 5 g of maltodextrin was added next. Once the maltodextrin had dissolved, the pH was adjusted to between 3.3 and 5.0 and the volume adjusted to 100 mL.

10. All solutions were kept in sealed glass bottles at room temperature in the dark after they were prepared (UDCA and carbohydrate in solution are sensitive to sunlight). The physical appearance of the solutions was visually inspected periodically.

11. The results obtained in the second set of experiments are presented in the following table. The referenced photographs are attached as Exhibit 2.

Composition[1]	Satoshi Sample	Difference in UDCA[2]	Photo ID Nos.	Description
9(A)(i)	23	None	M1.0-1[3], M1.0-2[3], M1.0-3[3]	This composition became cloudy gradually after preparation (M1.0-1). It became cloudier after about 4 months (M1.0-2). Then opalescent material settled to the bottom of the bottle leaving a mostly clear supernatant after 4-5 months (M1.0-3).
9(A)(ii)	23	None	M1.0-H[3]	This composition became cloudy gradually and then, became cloudier 4-5 months later.
9(A)(ii)	23	-100 mg	M0.9-H[3]	This composition became cloudy gradually and then, became cloudier 4-5 months later.
9(A)(iv)	23	- 200 mg	M0.8-H[3]	This composition became cloudy gradually and then, became cloudier 4-5 months later.
9(B)(i)	22	None	M0.6-1[3], M0.6-2[3]	This composition became cloudy within 3-4 months (M0.6-1) and cloudier 4-5 months later (M0.6-2).
9(B)(ii)	22	None	M0.6-H[3]	This composition became cloudy after 4-5 months
9(C)(i)	20	None	M1.0-20[3]	This composition became a thick milky solution upon cooling.
9(D)(i)	19	- 200 mg	M0.4-19[3]	This composition became a thick, milky solution upon cooling.
9(E)(i)	18	+ 200 mg	M0.3-18[3]	This composition became a thick, milky solution upon cooling.
9(F)(i)	15	None	M0.5-15[3]	This composition gradually became cloudy over a 4-5 month period.
9(G)(i)	15	None	M0.4-0.7	This composition became cloudy gradually and then, became cloudier 4-5 months later.
9(G)(ii)	15	- 100 mg	M0.4-0.7	This composition became cloudy gradually and then, became cloudier 4-5 months later.
9(H)(i)	22	None	M0.4-0.7	This composition became cloudy gradually and then, became cloudier 4-5 months later.
9(H)(ii)	22	+ 100 mg	M0.4-0.7	This composition became cloudy gradually and then, became cloudier 4-5 months later.
9(H)(iii)	22	+ 200 mg	M0.7-1.0	This composition became cloudy gradually and then, became cloudier 4-5 months later.
9(I)(i)	23	- 100 mg	M0.7-1.0	This composition became cloudy gradually and then, became cloudier 4-5 months later.
9(I)(ii)	23	None	M0.7-1.0	This composition became cloudy gradually and then, became cloudier 4-5 months later.

[1] Composition was prepared according to indicated paragraph of the present Declaration.
[2] Difference, if any, in amount of UDCA used in the Satoshi sample and the amount used in the present sample.
[3] Bottle on left contains reference solution described in paragraph 9(J)(i).

12. The foregoing results demonstrate that the disclosures of Satoshi are insufficient to enable the preparation of bile acid solutions that are stable for more than five months.

13. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made may jeopardize the validity of any patent issuing from the above-captioned patent application.

May 14, 2004
Date

SEO HONG YOO

[Translation from Japan se]

(19) Japanese Patent Office (JP)

(12) Official Gazette of Unexamined Patent Applications (A)

(11) Patent Application Publication No: **62-153220**

(43) Patent Application Publication Date: July 8, 1987

(51) Int. Cl.[4]	Identification Code	Internal File Nos.
A 61 K 31/575	ACT	7252-4C
// A 61 K 47/00	336	L-6742-4C

Request for Examination: Not Yet Received
Number of Inventions [Independent Claims]: 1 (Total of 7 Pages)

(54) Title of the Invention: **Water-Based Bile Acid Agent for Internal Use**

(21) Patent Application No: 60-292933

(22) Patent Application Date: December 27, 1985

(72) Inventor: Shinzo NAKAZAWA
1576, Yuki, Yuki-shi

(72) Inventor: Satoshi HISANO
1-36, Torikottobanchi, 2568, Horigome, Ashikaga-shi

(71) Applicant: Tokyo Tanabe Co., Ltd.
2-7-3, Nihonbashi-honcho, Chuo-ku, Tokyo

(74) Agent: Naoyuki MATSUYAMA, Patent Attorney

Clean Copy of Specification (Contents Unchanged)

Specification

1. Title of the Invention

Water-Based Bile Acid Agent for Internal Use

2 Claims

(1) A water-based bile acid agent for internal use, wherein the compounding weight ratio of dextrin to bile acid is 30:1 or higher and the dextrin concentration is 35% (W/W) or less in a water-based agent containing a bile acid and a dextrin.

(2) The water-based bile acid agent for internal use described in claim 1, wherein the bile acid is ursodeoxycholic acid or chenodeoxycholic acid.

(3) The water-based bile acid agent for internal use described in claim 2, wherein the dextrin is amylodextrin, maltodextrin or erythrodextrin.

3. Detailed Description of the Invention

Industrial Field of Application

[01] The present invention relates to a water-based bile acid agent for internal use containing a bile acid and a dextrin. The water-based bile acid agent for internal use in the present invention is a clear liquid agent in which the bile acid has been solubilized in water. Because this masks the extreme bitter taste of bile acid solids, it can be used as a bile acid medicine administered orally.

Prior Art

[02] Bile acid is widely used as a cholagogue, a medicine highly valued for its performance and effect. However, bile acid is not very soluble in water and has an extremely bitter taste. Therefore, it has been very difficult to develop a non-bitter bile acid aqueous solution. At the present time, this has hindered the preparation of a water-based agent for internal use that is easier for the digestive tract to absorb than a solid formulation such as a tablet or grains.

[03] Methods of the prior art used to obtain bile acid aqueous solution formulations include solubilizing bile acid in sodium salts (Japanese Examined Patent Application Publication [Kokoku] No. 35-17149) and solubilizing bile acid in clathrate compounds such as β-cyclodextrin (Japanese Unexamined Patent Application Publication [Kokai] No. 55-22616). One method of reducing the bitter taste of bile acid aqueous solutions is to use a sweetener such as sucrose or honey [Basic Course in Drug Development XI: Drug Preparation Methods (Part II), p. 706, Chijinshokan, 15 November 1971].

Problem Solved by the Invention

[04] However, because the solubility method using bile acid salts requires an aqueous solution value between 9.5 and 100, careful pH control is essential and it is difficult to obtain a water-based agent for internal use that is neutral or weakly acidic. In this method, moreover, the bitter taste in the bile acid aqueous solution is not completely eliminated and is sometimes strong. In the solubility

method using clathrate compounds, because the resulting clathrate compounds are bulky (apparent specific gravity 0.04 g/cc, scattering rate 38-45%) and in the form of a fine powder, they are extremely difficult to handle during preparation of the water-based agent for internal use and the scattering of bile acid may have an adverse effect on the health of workers preparing the formulation. The method of reducing the bittor taste of bile acid by using a sweetener also does not completely mask the bitter taste of bile acid in an aqueous solution and leaves an unpleasant aftertaste during oral administration. The bile acid, moreover, is not completely solubilized in syrup containing sucrose or honey, which is a fatal flaw. The present inventors have conducted extensive research on pharmaceutical additives for solubilizing and dispersing difficult-to-solubilize compounds. For example, they have conducted experimental preparation of bile acid aqueous solutions using macromolecular compounds such as sodium carboxymethylcellulose and hydroxypropylcellulose as well as surfactants such as stearic acid polyoxyl 40 and polyethylene glycol. In all of these tests, the solubility and bitter taste masking were never simultaneously adequate.

Means of Solving the Problem

[05] However, when preparing a bile acid aqueous solution using a common dextrin as a binder or formulation diluent, the present inventors surprisingly produced a clear aqueous solution in which the bile acid was completely solubilized and in which there was no bitter taste. The present invention is the product of this discovery.

[06] In other words, the present invention is a water-based bile acid agent for internal use, wherein the compounding weight ratio of dextrin to bile acid is 30:1 or higher and the dextrin concentration is 35% (W/W) or less in a water-based agent containing a bile acid and a dextrin (hereinafter referred to as the water-based agent of the present invention).

[07] The amount of bile acid contained in the water-based agent of the present invention can by anywhere within the range of pharmacological effectiveness for bile acid. The amount of dextrin in the water-based agent of the present invention should have a compounding weight ratio of 30:1 or higher with respect to the bile acid and an overall concentration in the water-based agent of 35% (W/W) or less. If (1) the compounding weight ratio is lower than 30:1, the bile acid does not solubilize sufficiently in the water and a water-based bile acid agent cannot be obtained. Furthermore, the bitter taste of the bile acid is not masked sufficiently. If (2) the dextrin concentration exceeds 35% (W/W), the bile acid does not solubilize adequately and the resulting aqueous solution is cloudy. Because an aqueous solution containing dextrin is essentially weakly acidic, the pH of the resulting water-based agent of the present invention can be adjusted relatively easily to obtain a neutral or weakly acidic water-based agent for internal use.

[08] The bile acids that can be used are ursodeoxycholic acid and chenodeoxycholic acid. The dextrins that can be used are amylodextrin, maltodextrin and erythrodextrin.

[09] The essential ingredients of the water-based agent of the present invention are bile acid, dextrin and water. In addition to these three ingredients, other additives can be included during preparation of the agent. These include binding agents such as hydroxypropylcellulose and polyvinylpyrolidone, surfactants such as stearic acid polyoxyl 40, polyoxyothylene-hardened castor oil 60 and propylene glycol, and a small amount of ethanol. Other medicinal additives include preservatives to preserve the bile acid, flavorings and sweeteners. If necessary, supplemental preservatives can be added. Examples of preservatives include butyl paraoxybenzoate, propyl paraoxybenzoate or dehydroacetic acid. Examples of sweeteners include sucrose, glucose, sodium citrate and sodium phosphate. Flavorings include menthol, orange flavoring, strawberry flavoring, vanilla flavoring, liquid cinnamon and plum flavoring. Supplemental preservatives include citric acid, hydrochloric acid and phosphoric acid.

[10] Effective ingredients that supplement the bile acid can be added to the water-based agent of the present invention These include fortifying agents such as γ-olizanol, taurine and royal jelly; vitamins such as thiamine chloride, riboflavin, hydroxine chloride, ascorbic acid, tocophenol, biotin and calcium

pantothenate; and natural medicinals such as gentian, cinnamon, vervain, licorice, ginger, fennel and carrot.

[11] In the water-based agent of the present invention, 1 ppw bile acid and 30 ppw or more dextrin are mixed together in a fluidized bed. While the appropriate amount of binding solution is sprayed on the bed, this mixture is granulized at a circulating warm air temperature of 50-80°C. Water is added, and the grains are stirred and dissolved in the water at a temperature of 15-70°C. The solution can be adjusted at the same temperature using water until the final concentration of dextrin is 35% (W/W) or less. (Hereinafter, this method is referred to as the fluidized-bed granulation method.) An appropriate binding solution is a binding agent such as water or hydroxypropylcellulose and polyvinylpyrolidone or an aqueous solution or ethanol aqueous solution containing a surfactant such as stearic acid polyoxyl 40, polyoxyethylene-hardened castor oil 60 or polypropylene glycol. In the granulation stage of the fluidized-bed granulation method, the resulting grains have extremely low scattering properties. In other words, the grains obtained in this manner have an apparent specific gravity 0.35-0.61 g/cc and a scattering rate of 8-13%.

[12] Also, after evenly dispersing 1 ppw bile acid in water, 30 ppw or more dextrin can be added to the dispersant, stirred and dissolved at 15-70°C, and adjusted at the same temperature with water so the final concentration of dextrin is 35% (W/W) or less. (This method is hereinafter referred to as the dispersal method.) In the stage of the dispersal method where the bile acid dispersant is

obtained, the bile acid (apparent specific gravity 0.18-0.25 g/cc, scattering rate 15-24%) can be simply added or dissolved in ethanol to improve the dispersion properties before being added. If necessary, a surfactant such as stearic acid polyoxyl 40, polyoxyethylene-hardened castor oil 60 or polypropylene glycol can be added.

[13] Compared to the method of solubilizing bile acid in clathrate compounds (apparent specific gravity 0.04 g/cc, scattering rate 38-44%) (Kokai No. 55-22616), the clear water-based bile acid agents for internal used obtained using the fluidized-bed granulation method and dispersal method pose less risk of scattering bile acid and are easier to handle.

[14] When preservatives, sweeteners, flavorings, supplemental preservatives and other additives are used in the water-based agent of the present invention, they are added in the granulation stage of the fluidized-bed granulation method and in the stage where the bile acid dispersant is obtained in the dispersal method. However, the medicinal additives can be added in the bile acid solubilizing stage of both methods after the bile acid has been stirred and dissolved. If other active ingredients are to be included in the water-based agent of the present invention in addition to bile acid, they too should be added in the bile acid solubilizing stage of both methods. These active ingredients can be added alone or in an aqueous solution or aqueous suspension of vitamins and

nutrients. These can include natural medicinals such as plant extracts, liquid plant extracts, and plant tinctures.

Operation and Effect of the Invention

[15] The following is an explanation of the bile acid solubilizing effect and bitter taste masking effect of dextrin in the water-based agent of the present invention.

[16] In a test of bile acid solubilizing effects and bitter taste masking effects, 70 different samples were prepared and used. In this test, varying amounts of ursodeoxycholic acid (apparent specific gravity 0.24 g/cc, scattering rate 17%) or chenodeoxycholic acid (apparent specific gravity 0.19 g/cc, scattering rate 22%) were dispersed evenly in distilled water, varying amounts of amylodextrin, erythrodextrin or maltodextrin were added, the solution was stirred and mixed at 20-65°C, and the sample was adjusted with water at the same temperature to a total weight of 100 g. The various components in these samples except for the water are shown in the water-based agent composition lines of Table 1 and Table 2. These samples were adjusted so that the pH was between 3.3 and 5.0, that is, weakly acidic.

[17] The bile acid solubilizing effect was determined by measuring the light absorptivity of the samples at 660 nm using a spectrophotometer and by examining the samples with the naked eye to see if they were clear. The bitter taste masking effect was determined in a bitterness taste test with 10 panelists.

[18] The results from the bile acid solubilizing test and bitter taste masking test are shown in Table 1 and Tabl 2. In the clearness test using the naked eye, + means cloudy, ± means somowhat cloudy, and - means clear. In the bitter taste-masking test, the panelists placed 10 g of each sample in their mouths for 20 seconds to determine if they could taste any bitterness. Here, O means all ten panelists perceived no bitterness, Δ means 1 to 7 panelists perceived some bitterness, and x means 8 or more panelists perceived some bitterness. In both tests, the ratio of dextrin to bile acid in the samples was the significant factor.

(This space left intentionally blank.)

FIG 1

Sample No.		1	2	3	4	5	6	7	8	9	10
Agent Composition	Ursodecxycholic Acid (mg)	12	30	120	200	240	120	200	240	12	25
	Amylodextrin (g)	6	6	6	6	6				15	15
	Maltodextrin (g)						6	6	6		
	Dextrin Concentration % (W/W)	6	6	6	6	6	6	6	6	15	15
	Compounding Ratio	500	200	50	30	25	50	30	25	1250	600
Solubility Effect	Light Absorptivity	0.006	0.008	0.012	0.058	0.302	0.050	0.088	0.492	0.006	0.008
	Clarity	-	-	-	-	±	-	-	+	-	-
Bitterness Masking Effect		O	O	O	O	Δ	O	O	Δ	O	O

FIG 1 (Continued)

Sample No.		11	12	13	14	15	16	17	18	19	20
Agent Composition	Ursodeoxycholic Acid (mg)	250	500	600	250	500	600	60	100	600	1000
	Amylodextrin (g)	15	15	15				30	30	30	30
	Maltodextrin (g)				15	15	15				
	Dextrin Concentration % (W/W)	15	15	15	15	15	15	30	30	30	30
	Compounding Ratio	60	30	25	60	30	25	500	300	50	30
Solubility Effect	Light Absorptivity	0.032	0.084	0.66	0.048	0.092	0.78	0.008	0.010	0.088	0.084
	Clarity	-	-	+	-	-	+	-	-	-	-
Bitterness Masking Effect		O	O	Δ	O	O	Δ	O	O	O	O

FIG 1 (Continued)

Sample No.		21	22	23	24	25	26	27	28	29	30
Agent Composition	Ursodeoxycholic Acid (mg)	1200	600	1000	1200	70	233	437	1167	1750	437
	Amylodextrin (g)	30				35	35	35	35	35	
	Maltodextrin (g)		30	30	30						35
	Dextrin Concentration % (W/W)	30	30	30	30	35	35	35	35	35	35
	Compounding Ratio	25	50	30	25	500	150	60	30	20	80
Solubility Effect	Light Absorptivity	0.89	0.090	0.102	0.98	0.022	0.074	0.088	0.101	1.1	0.100
	Clarity	!	-	-	+	-	-	-	-	+	-
Bitterness Masking Effect		Δ	O	O	Δ	O	O	O	O	Δ	O

FIG 1 (Continued)

Sample No.		31	32	33	34	35	36	37	38	39	40
Agent Composition	Ursodeoxycholic Acid (mg)	1167	1750	80	200	400	500	800	80	200	400
	Amylodextrin (g)			40	40	40	40	40			
	Maltodextrin (g)	35	35						40	40	40
	Dextrin Concentration % (W/W)	35	35	40	40	40	40	40	40	40	40
	Compounding Ratio	33	20	500	200	100	80	50	500	200	100
Solubility Effect	Light Absorptivity	0.102	1.3	0.264	0.62	0.98	1.4	1.5	0.428	0.84	0.96
	Clarity	-	+	=	+	+	+	+	+	+	+
Bitterness Masking Effect		O	Δ	O	Δ	Δ	×	×	O	Δ	×

FIG 2

Sample No.		41	42	43	44	45	46	47	48	49	50
Agent Composition	Chenodeoxycholic Acid (mg)	25	100	250	333	400	250	333	400	60	100
	Amylodextrin (g)	10	10	10	10	10				30	30
	Erythrodextrin (g)						10	10	10		
	Dextrin Concentration % (W/W)	10	10	10	10	10	10	10	10	30	30
	Compounding Ratio	400	100	40	30	25	40	30	25	500	300
Solubility Effect	Light Absorptivity	0.008	0.008	0.022	0.070	0.505	0.040	0.066	0.666	0.010	0.022
	Clarity	-	-	-	-	+	-	-	+	-	-
Bitterness Masking Effect		O	O	O	O	Δ	O	O	Δ	O	O

FIG 2 (Continued)

Sample No.		51	52	53	54	55	56	57	58	59	60
Agent Composition	Chenodeoxycholic Acid (mg)	600	100	1200	1000	1200	70	233	467	1167	1750
	Amylodextrin (g)	30	30	30			35	35	35	35	35
	Erythrodextrin (g)				30	30					
	Dextrin Concentration % (W/W)	30	30	30	30	30	35	35	35	35	35
	Compounding Ratio	50	30	25	30	25	500	150	80	30	20
Solubility Effect	Light Absorptivity	0.094	0.100	0.92	0.098	1.1	0.009	0.048	0.100	0.102	1.2
	Clarity	-	-	+	-	+	-	-	-	-	+
Bitterness Masking Effect		O	O	Δ	O	Δ	O	O	O	O	×

FIG 2 (Continued)

Sample No.		61	62	63	64	65	66	67	68	69	70
Agent Composition	Chenodeoxycholic Acid (mg)	1167	1750	80	200	400	500	800	80	200	400
	Amylodextrin (g)			40	40	40	40	40			
	Erythrodextrin (g)	35	35						40	40	40
	Dextrin Concentration % (W/W)	35	35	40	40	40	40	40	40	40	40
	Compounding Ratio	30	20	500	200	100	80	50	500	200	100
Solubility Effect	Light Absorptivity	0.104	1.4	0.338	0.74	0.98	1.3	1.8	0.56	0.80	1.2
	Clarity	-	+	±	+	+	+	+	+	+	+
Bitterness Masking Effect		O	x	O	Δ	x	x	x	O	Δ	x

(This space left intentionally blank.)

[19] As can be seen in Table 1 and Table 2, the water-based bile acid agents for internal use in which the compounding weight ratio of dextrin to bile acid is 30:1 or higher and in which the dextrin concentration is 35% (W/W) or less are clear aqueous solutions in which the bile acid has been solubilized in the water to a remarkable degree, in which the light absorptivity is less than 0.1, and in which the bitter taste of the bile acid solids has been sufficiently masked. As a result, the water-based bile acid agents of the present invention can be used as non-bitter water-based agents for internal use.

[20] Most of the samples described above correspond to working examples of the present invention. However, in order to explain the present invention further, the following is a description of additional working examples.

Working Example 1

[21] First, 10 g of ursodeoxycholic acid and 1 g of butyl paraoxybenzoate were solubilized in ethanol to obtain exactly 100 ml of solution. Next, 1 ml of the ethanol solution was measured out using a measuring pipette, introduced to 80 g of sterilized water, and dispersed evenly. Next, 3 g of amylodextrin was added to the dispersant and then stirred and mixed evenly at a temperature of 60-65°C. When the amylodextrin was added, the cloudy dispersant immediately became clear and the bitter taste was completely imperceptible.

[22] Next, to the aqueous solution were added 350 mg of licorice extract, 0.8 ml of liquid ginger extract, 1.5 ml of fennel extract, 0.5 ml of liquid cinnamon

extract, 130 mg of carrot extract, 0.1 ml of plum flavoring, 10 g of glucose, and 0.5 g of polyoxyethylene-hardened castor oil 60. The contents were stirred and mixed thoroughly, the solution was passed through a 0.45 μ membrane filter for sterilization filtration, and sterilized water was added to the filtered solution until the total amount was 100 g. The resulting solution was divided evenly in five 20 ml drink containers, which were then sealed with metal caps to obtain an orally administered gastrointestinal agent. When the amount of ursodeoxycholic acid in each container was measured using gas chromatography, the results were 19.8 ± 0.3 mg.

Working Example 2

[23] First, 5 g of chenodeoxycholic acid (apparent specific gravity 0.18 g/cc, scattering rate 24%) and 490 g maltodextrin were measured out and added to a Freund FLO-1 fluidized-bed granulator for mixing. While spraying 100 g of a 40% (W/W) aqueous ethanol solution containing 1% (W/W) hydroxyproylcellulose into the fluidized bed, fluidized-bed granulation was performed at a circulating warm air temperature of 60°C and the resulting grains were sized to 32 mesh. The resulting grains had an apparent specific gravity of 0.41 g/cc and a scattering rate of 10%.

[24] When 32 g of the grains were added to 80 g of sterilized water and mixed in thoroughly, the resulting clear aqueous solution had no bitter taste and was somewhat sweet tasting. Next, 1 ml of an ethanol aqueous solution containing 1% (W/V) butyl paraoxybenzoate and 0.5 g of stearic acid polyoxyl 40 were added to the aqueous solution, stirred and mixed thoroughly, and added to

sterilized water to reach a total weight of 120 g. The resulting solution was divided evenly in four 30 ml drink containers, which were then sealed with metal caps to obtain an orally administered agent. When the amount of chenodeoxycholic acid in each container was measured using gas chromatography, the results were 79.5 ± 0.8 mg.

Working Example 3

[25] First, 5 g of ursodeoxycholic acid (apparent specific gravity 0.25 g/cc, scattering rate 15%) and 395 g erythrodextrin were measured out and added to a Freund FLO-1 fluidized-bed granulator for mixing. While spraying 80 g of water into the fluidized bed, fluidized-bed granulation was performed at a circulating warm air temperature of 60°C and the resulting grains were sized to 32 mesh. The resulting grains had an apparent specific gravity of 0.57 g/cc and a scattering rate of 9%.

[26] When 4 g of these grains were added to 70 g of sterilized water and stirred in thoroughly, a clear aqueous solution was obtained with no bitter taste at all.

[27] Next, to the aqueous solution were added 20 mg of thiamine chloride, 10 mg of tocopherol acetate, 5 mg of riboflavin phosphate, 50 μg of biotin, 1000 mg of taurine, 250 mg of royal jelly, 15 g of sucrose, 0.1 ml of propylene glycol, and 0.1 ml of orange flavoring. After thorough mixing, the solution was adjusted with sterilized water to a total weight of 100 g. The contents were stirred and mixed

thoroughly and th solution was then passed through a 0.45 μ membrane filter for sterilization filtration. The resulting solution was divided evenly in five 20 ml drink containers, which were then sealed with metal caps to obtain an orally administered nutrient enriched agent. When the amount of ursodeoxycholic acid in each container was measured using gas chromatography, the results were 9.9 ± 0.2 mg.

Applicant Tokyo Tanabe Co., Ltd.

Agent Naoyuki MATSUYAMA, Patent Attorney

Amendment of Proceedings (Filed by Applicant)

February 18, 1986

To the Honorable Michio UGA, Director-General of the Japanese Patent Office

1. Application
   Patent Application No. 60-292933

2. Title of the Invention
   Water-Based Bile Acid Agent for Internal Use

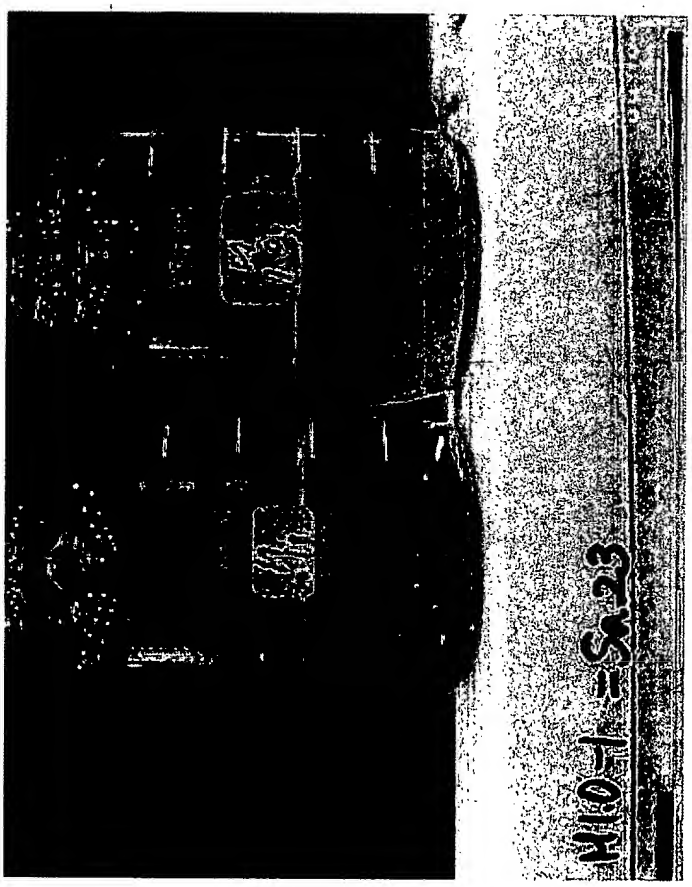
3. Party Filing the Amendment
   Relation to Case: Patent Applicant
   Name: Tokyo Tanabe Co., Ltd.
   Address: 2-7-3, Nihonbashi-honcho, Chuo-ku, Tokyo

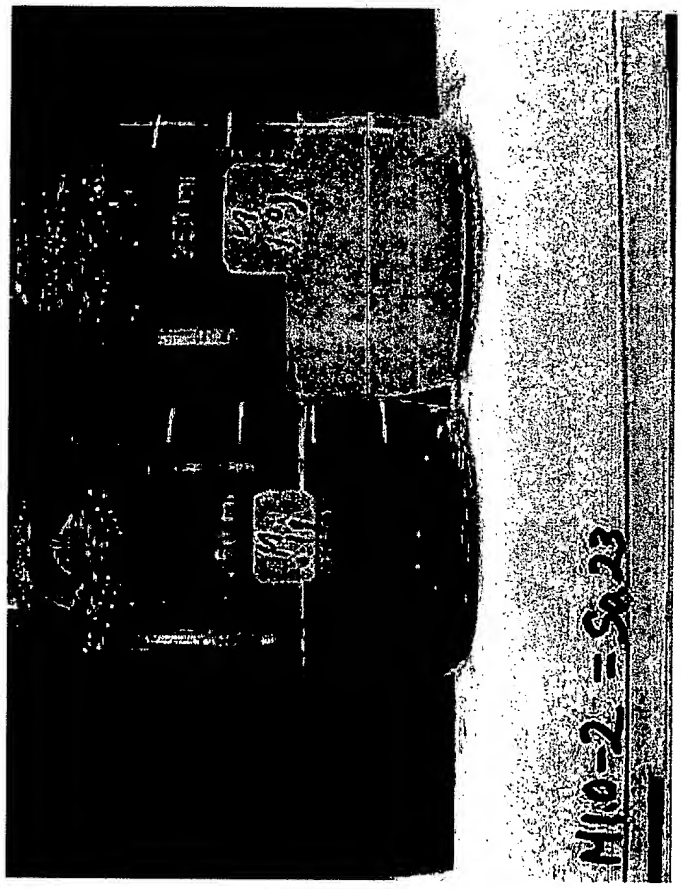
4. Representative
   Name: Naoyuki MATSUYAMA, Patent Attorney (9283)
   Address: Tokyo Tanabe Research and Development Office
   2-33-3, Akabanekita, Kita-ku, Tokyo 115
   Telephone: 03 (907) 1331

6. Section to be Amended: Entire Specification

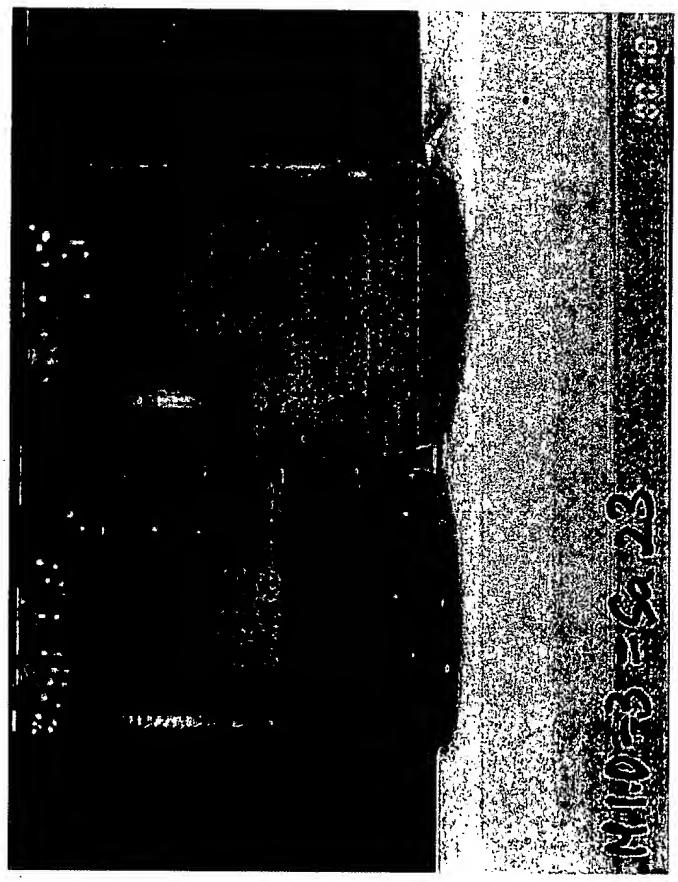
8. Content of the Amendment: See Attachment
   Clean Copy of Specification (Contents Unchanged)

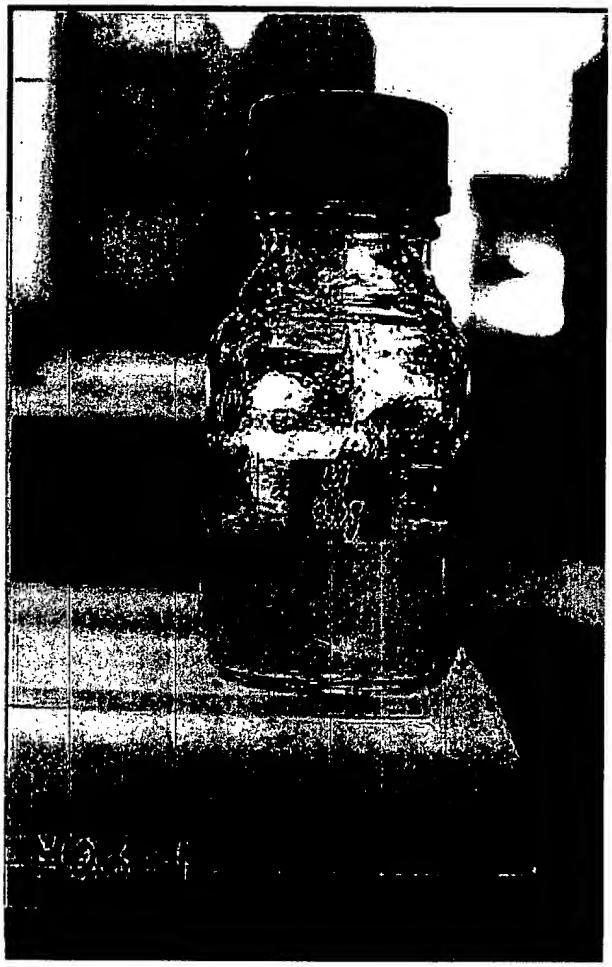
[Received by JPO, February 18, 1986]

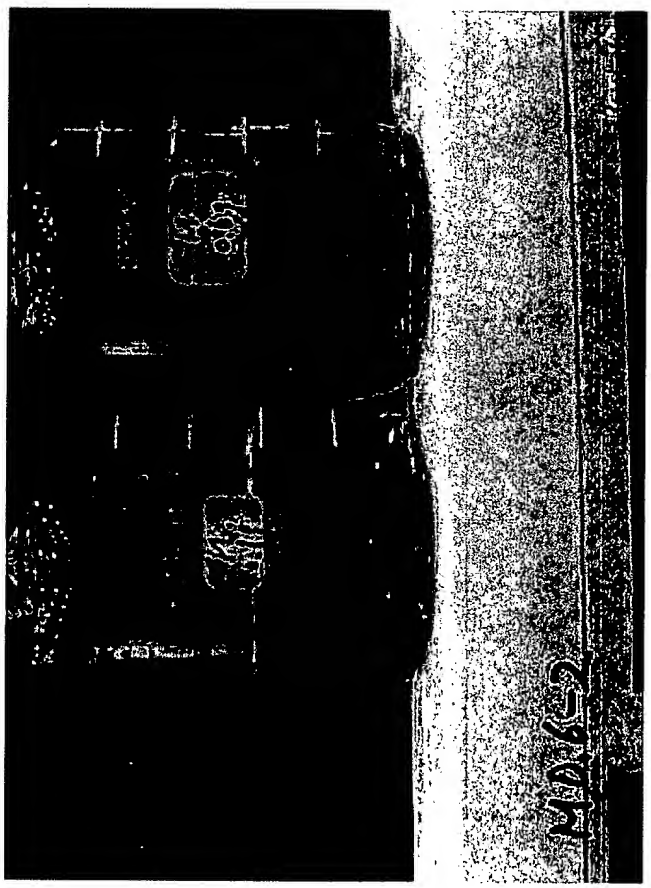


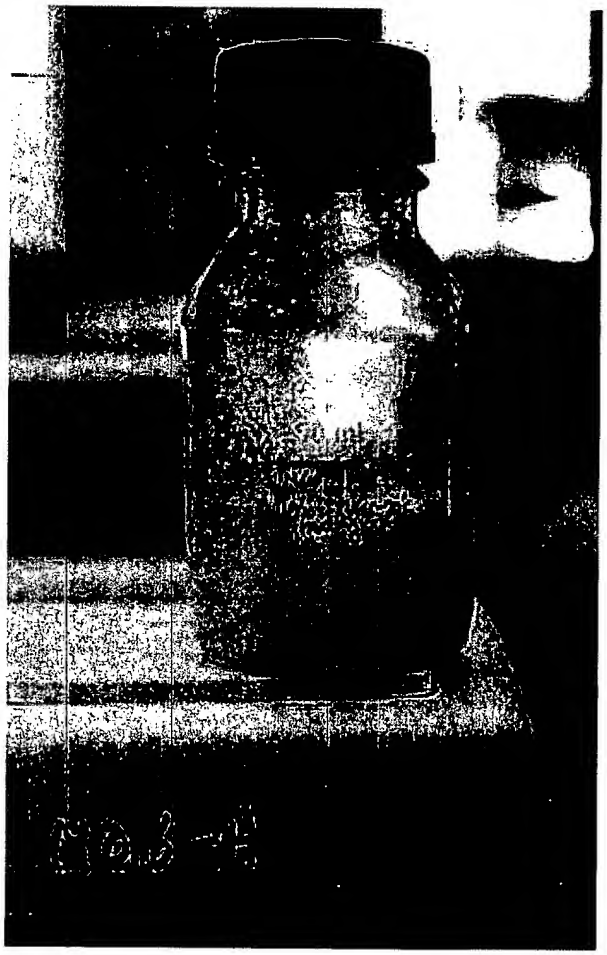


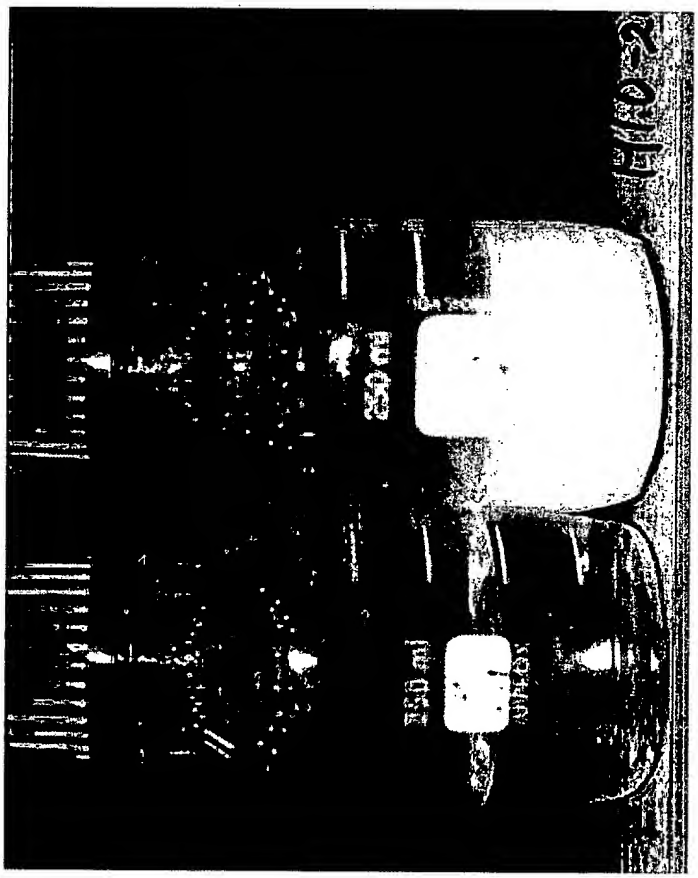
BEST AVAILABLE COPY

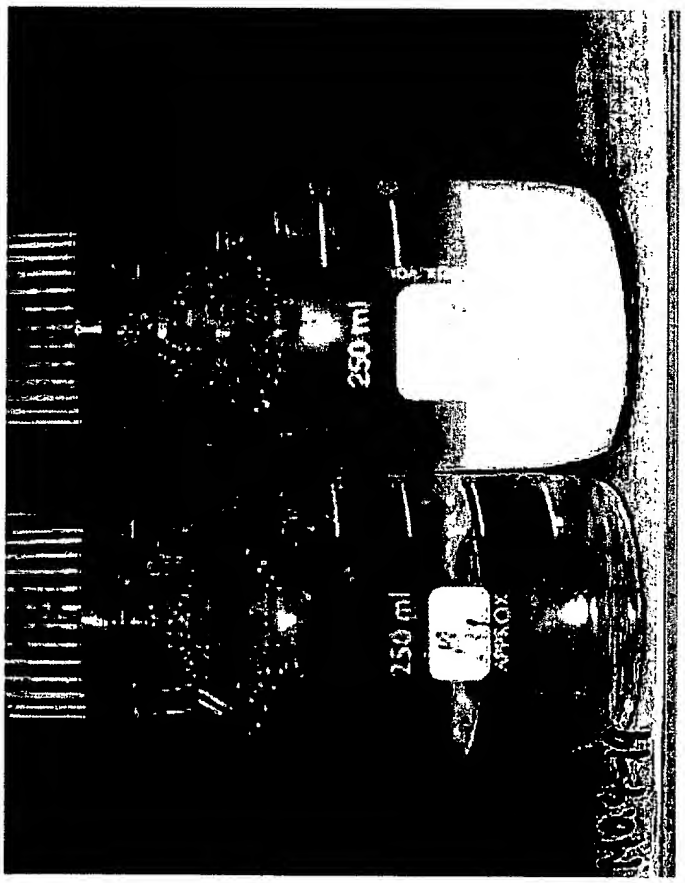












BEST AVAILABLE COPY